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Original Article Open Access

Effect of omega-3 fatty acid supplementation on nutritional status in patients with gastric cancer during chemotherapy

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Article History
Received:
14/04/2014
Revised:
29/05/2014
Accepted:
19/06/2014

Keywords:
Omega 3 fatty acid,
Weight,
Nutrition,
Gastric cancer,
Chemotherapy

ABSTRACT

Background: Although some studies have shown positive effects of omega-3 fatty acid supplementation on nutritional status of cancer patients undergoing different treatments, there is no consistency in results. The aim of this study was to examine the effects of omega-3 fatty acid on the nutritional status of gastric cancer patients during the course of chemotherapy.

Methods: In a double-blind clinical trial, 30 adult patients with gastric cancer receiving chemotherapy were randomized into a supplement and a placebo groups and given daily, for 6 weeks, a 3-g omega-3 fatty acid supplement (containing 1.8g eicosapentaeonic plus 1.2g docosahexaenoic acid) and oral paraffin, respectively. Anthropometric data was collected and nutritional status assessed at the beginning, at week 4 and at the end of week 6. The data were analyzed using repeated measures ANOVA and independent sample t-test.

Results: The findings indicated that omega-3 fatty acid supplementation increased body weight, mean daily intake of energy and macronutrients, serum levels of transferrin and albumin at the end of the 6-week period significantly ($p<0.05$). All these variables decreased in the placebo group ($p<0.05$). The increases in body weight, energy and carbohydrate intakes, and serum levels of albumin in the supplement group were time-dependent ($p<0.05$).

Conclusion: The results of present study showed that omega-3 fatty acid supplementation can improve nutritional status in patients with gastric cancer during the course of chemotherapy. We recommend using omega-3 fatty acid supplement in patients with gastric cancer during chemotherapy.

Introduction

The global incidence of malnutrition in cancer patients ranges from 30% to 85%, being most prevalent in patients with gastric, pancreatic, lung, prostate and colon cancer [1,2]. Besides several variables such as age, gender and individual susceptibilities, malnutrition also affects anticancer treatments and disease symptoms. Prolonged under-nutrition can result in cachexia, involuntary body weight loss with depletion of lean body mass, muscle wasting,

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weakness [3], impaired response to chemotherapy [4,5], susceptibility to chemotherapy-induced toxicity [5,6], decrement of life quality and increment of morbidity and mortality [7]. An inadequate nutritional intake occurs frequently in cancer patients who fail to cope with increasing resting energy demands. The reduced food intake and metabolic change are vitally important in patients with cancer cachexia [8]. Providing nutritional support may be useful in aspect of minimizing gastrointestinal symptoms and improving life quality. Nutritional supplementation in adequately nourished patients delays the progression of malnutrition [9], improves immune function [2,10] and performance status [11,12]. It has been shown that the fish oil inhibits inflammation *in vivo* and is associated with weight gain, better response to therapy, fewer complications and even improved survival in some patients [13,14]. Studies on animals are quite promising, indicating that omega-3 fatty acid may be a clinically useful supplement to cancer therapy. The dose of omega-3 fatty acid used in animal studies have been very high, often 20–24% (by weight) of the diet. However, their results may convince the clinical researchers to use omega-3 fatty acid supplements for human treatment, although the mechanism of action is still under investigation and the optimum level of omega-3 fatty acids to suppress cancer growth [15] is yet to be determined. In this study, we examined effects of omega-3 fatty acid intake on anthropometric measurements, biochemical factors and food intake in patients with gastric cancer during chemotherapy.

Methods

Study design and population

This double blind clinical trial study was conducted in Nutrition Research Center of Tabriz University of Medical Sciences, Iran, 2010 - 2011. The study was approved by the Medical Ethical Committee of the Tabriz University of Medical Sciences and registered under identification code of IRCT 201011095144N1 in Iranian Registry of Clinical Trials. Thirty adult patients over 30 years old at different stages of malignancies of gastric cancer undergoing chemotherapy were randomly selected from Imam and Fatemi Hospitals of Ardabil city. The aims and study protocol were explained to the subjects and a written consent was taken from all participants. Only patients over 30 years old were selected and were divided into two groups of supplement and placebo. Subjects with diseases inducing cachexia such as heart, lung and renal diseases, AIDS, acute leukemia, diabetes, multiple myeloma, and individuals undergoing surgery were excluded. The staging procedure, based on imaging results of cancer, was used for patients with gastric cancer, and only stages II and III were included in the study. Data on anthropometric indices and biochemical parameters were collected in the beginning, middle and at the end of the chemotherapy period, and changes in weight, body mass index (BMI), and biochemical parameters were calculated for both groups. The supplement group received 3 times daily for 6 weeks, 3g omega-3 fatty acids (containing 1.8g eicosapentaenoic (EPA) and 1.2g docosahexaenoic acid (DHA)) (Herron-Sigma) in 10g fish oil, while the placebo group were given paraffin. Each tablet containing of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) was 180 mg and 120 mg in 1 gram fish oil, respectively. Fasting blood samples were taken at the beginning and after 4 and 6 weeks by venipuncture and the sera separated. All samples were kept frozen at – 80 ^{0}C until analyzed. Also, at the beginning and after 4 and 6 weeks, the nutritional status of the subjects was assessed using anthropometric measurements such as height, weight (current and usual weight), biochemical parameters (albumin and transferrin), and food intake determined. The BMI was calculated using the data recorded for height and weight.

Treatment schedule

The chemotherapy regimen consisted of 3 weeks of interval docetaxel (Taxotere; Sanofi-aventis, Bridgewater, NJ) 75 mg/m^2 (day 1) plus cisplatin 75 mg/m^2 (day 1) and fluorouracil 750 mg/m^2/d continuous infusion (days 1 to 5; DCF) according to Ajani's protocol [16].

Nutritional assessment

The usual body weight of the patients was asked and recorded at the start of the study. Body weight and BMI were measured for all patients at the beginning, middle and at the end of the study. Height and weight were obtained using a portable digital scale and portable digital stadiometer. Food intake changes were recorded using 24-hour dietary recalls for three days (2 weekdays and 1 weekend day) before treatment, and 4 and 6 weeks after intervention. Mean daily dietary intake and food composition were

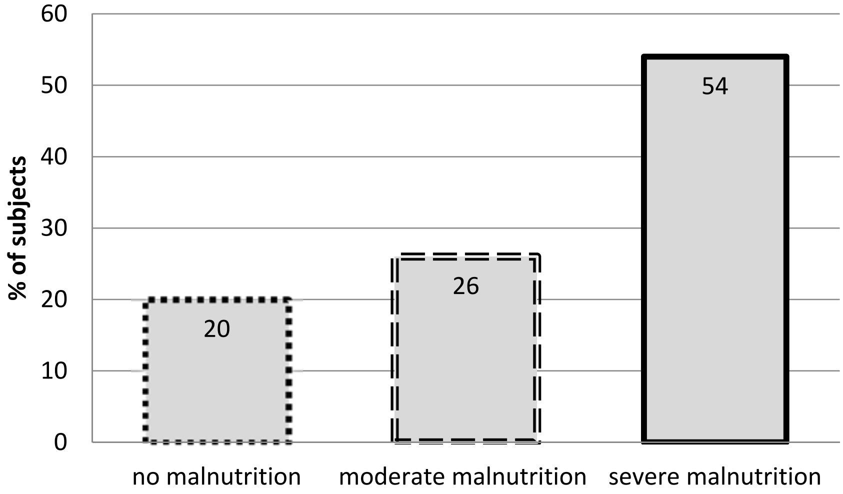

Figure 1. Nutritional status of the subjects before the intervention

estimated using Nutritionist IV. Fasting blood samples were taken for measurement of transferrin and albumin before treatment, 4 and 6 weeks after intervention. Serum albumin and transferrin concentrations were measured by routine laboratory procedures. For all volunteers the nutritional risk index (NRI) was determined before intervention using the formula NRI= (1.489 × serum albumin, g/l) +41.7 × (current weight/usual weight)

A NRI>100 indicates that the patient is not malnourished, 97.5-100 indicates mild, 83.5-97.5 moderate and <83.5 severe malnourishment [17,18].

Statistical analysis

Repeated measures ANOVA, paired sample t-test and independent sample t-test were used for data analysis in SPSS (version 14). Results are expressed as mean ± SD. Significant changes were assumed significant at p<0.05.

Results

Most of the patients with gastric cancer undergoing chemotherapy had moderate to severe malnutrition (Fig. 1.) The biochemical and anthropometric variables at different times are shown in Table 1. The results indicated that, as compared to the placebo group, omega 3 fatty acids significantly increased body weight and mean serum levels of transferrin and albumin of patients in the supplement group (in all cases p<0.05).

Table 1. Comparison of anthropometric and biochemical variables between the supplement and placebo groups

	Time measured	Supplement (n=15)	Placebo (n=15)	p-value
Weight (kg)	Before intervention	56.7 ± 10.2	56.2 ± 6.9	0.86
	After 4 weeks	58.3 ± 9.4*	54.3 ± 6.6*	0.18
	End of Week 6	59.2 ± 8.9**	52.6 ± 5.6**	0.02•
BMI (kg/m^2)	Before intervention	20.4 ± 2.7	20.6 ± 2.6	0.85
	After 4 weeks	20.9 ± 2.5*	19.9 ± 2.4*	0.26
	End of Week 6	21.1 ± 2.4**	19.5 ± 2.4**	0.08
Serum albumin (mg/dl)	Before intervention	3.82 ± 0.22	3.87 ± 0.26	0.56
	After 4 weeks	3.88 ± 0.26	3.93 ± 0.24	0.61
	End of Week 6	4.1 ± 0.34**	3.86 ± 0.25	0.01•
Serum transferrin (mg/dl)	Before intervention	226.8	245.7	0.052
	After 4 weeks	228.4	231.4	0.75
	End of Week 6	242.4	214.8**	0.03•

*Values are mean ±SD, *P <0.05 vs baseline, ** P<0.05 vs 4 weeks*
•p <0.05 in independent sample T-test between the two groups

Table 2. Comparison of daily energy, macronutrients, fiber and cholesterol intakes between the placebo and supplement groups during the study

Variables	Time measured	Supplement (n=15)	Placebo (n=15)	p-value
Energy (kcal/day)	Before	1651 ± 183	1734 ± 164	0.2
	After 4 weeks	1692 ± 180*	1597 ± 183*	0.16
	End of Week 6	1793 ± 130**	1408 ± 255**	0.01•
CHO (g/day)	Before	232 ± 40	267 ± 33	0.14
	After 4 weeks	259 ± 30*	258 ± 35	0.92
	End of Week 6	269 ± 37*	218 ± 48**	0.03•
Fat (g/day)	Before	47 ± 11	49 ± 16	0.81
	After 4 weeks	47 ± 11	45 ± 10*	0.16
	End of Week 6	49 ± 11	38 ± 12*	0.01
Protein (g/day)	Before	73 ± 22	58 ± 20	0.055
	After 4 weeks	74 ± 22	57 ± 15	0.02•
	End of Week 6	75 ± 14	49 ± 18	0.01•
Saturated fatty acids (g/day)	Before	10 ± 3	11 ± 6	0.71
	After 4 weeks	11 ± 5	9 ± 4	0.58
	End of Week 6	12 ± 4	8 ± 3	0.04•
Polyunsaturated fatty acid(g/day)	Before	6 ± 2	6 ± 3	0.07
	After 4 weeks	6 ± 2	5 ± 2	0.49
	End of Week 6	7 ± 3	5 ± 2	0.02•
Monounsaturated fatty acid(g/day)	Before	12 ± 4	12 ± 5	0.06
	After 4 weeks	14 ± 5	11 ± 4	0.8
	End of Week 6	15 ± 4	11 ± 4	0.03•
Fiber (g/day)	Before	7 ± 4	6 ± 2	0.27
	After 4 weeks	7 ± 1	6 ± 2	0.38
	End of Week 6	8 ± 3	5 ± 2	0.02•
Cholesterol (mg/day)	Before	210 ± 135	164 ± 117	0.08
	After 4 weeks	254 ± 115	125 ± 52	0.03•
	End of Week 6	274 ± 208	121 ± 39	0.01•
EPA (g/day)	Before	0.007 ± 0.003	0.0075 ± 0.001	0.41
	After 4 weeks	0.008 ± 0.003	0.007 ± 0.0027	0.58
	End of Week 6	0.0085 ± 0.0002	0.0069 ± 0.0001	0.14
DHA (g/day)	Before	0.0055 ± 0.0011	0.0059 ± 0.0012	0.06
	After 4 weeks	0.0059 ± 0.003	0.0052 ± 0.0027	0.8
	End of Week 6	0.0061 ± 0.0001	0.0051 ± 0.0001	0.13

*CHO= Carbohydrate, Pr= Protein, Values are mean ±SD, *p<0.05 vs baseline, ** p<0.05 vs4 weeks in Repeated Measures ANOVA, •p<0.05 in independent sample T-test between the two groups*

The body weight and energy and carbohydrate intakes, as well as serum levels of albumin also significantly increased in the supplemented group during the study ($p<0.05$), while they decreased in the placebo group during study period ($p<0.05$). The mean daily intakes of energy, carbohydrate, fat, protein, fatty acids (saturated, monounsaturated, and polyunsaturated fatty acids), fiber, and cholesterol in the supplemented group were higher than in the placebo group at the end of study ($p<0.05$) (Table 2). There was no significant difference between the two groups in terms of mean dietary omega-3 fatty acids. Daily micronutrient intakes of the subjects are shown in Table 3. It is seen that the mean daily intakes of vitamin A, potassium, copper and selenium in the supplement group were significantly higher than those in the placebo group at the end of week 6 ($p<0.05$); in the case of other nutrients no significant differences were observed.

Discussion

Our findings showed that 80% of the patients had moderate to severe malnutrition which is consistent with reports from previous studies [1-2, 19]. Malnutrition can lead to increased risk of morbidity, decline in chemotherapy response and weakness of the immune system, as well as shorter survivals in cancer patients [20]. Various nutritional interventions for the prevention of malnutrition have been performed in gastric cancer patients [21,22]. Dietary omega-3 fatty acid supplementation is recommended for them [23]. These fatty acids, present in large amounts in fish oil, actively reduce either tumor growth

Table 3. Comparison of daily vitamin and mineral intakes between the placebo and supplement groups during the study

Variables	Time measured	Supplement (n=15)	Placebo (n=15)	p-value
Vitamin A (RE/day)	Before	244 ± 108	316 ± 171	0.06
	After 4 weeks	248 ± 108	182 ± 177*	0.002
	End of Week 6	354 ± 273*	118 ± 93**	0.00•
Vitamin E (mg/day)	Before	10 ± 3	9 ± 3	0.16
	After 4 weeks	11 ± 3	9 ± 3	0.43
	End of Week 6	11 ± 3	9 ± 3	0.77
Vitamin C (mg/day)	Before	36 ± 20	37 ± 13	0.67
	After 4 weeks	40 ± 16	32 ± 29	0.17
	End of Week 6	43 ± 23	30 ± 8	0.02•
Vitamin B1 (mg/day)	Before	1.1 ± 0.18	1.1 ± 0.28	0.67
	After 4 weeks	1.2 ± 0.23	1.1 ± 0.25	0.25
	End of Week 6	1.2 ± 0.25	0.9 ± 0.23	0.01•
Vitamin B2 (mg/day)	Before	1.1 ± 0.84	0.99 ± 0.39	0.2
	After 4 weeks	1.1 ± 0.3	0.65 ± 0.25	0.03•
	End of Week 6	1.4 ± 0.83	0.59 ± 0.19	0.01•
Vitamin B3 (mg/day)	Before	20 ± 5	17 ± 6	0.14
	After 4 weeks	21 ± 10	19 ± 7	0.43
	End of Week 6	23 ± 15	14 ± 8	0.04•
Vitamin B5 (mg/day)	Before	2.1 ± 0.94	2.2 ± 1.2	0.22
	After 4 weeks	2.4 ± 0.96	1.6 ± 0.69	0.07
	End of Week 6	3.1 ± 2.7	1 ± 0.39	0.01•
Vitamin B6 (mg/day)	Before	0.73 ± 0.37	0.72 ± 0.46	0.24
	After 4 weeks	0.76 ± 0.32	0.70 ± 0.39	0.85
	End of Week 6	0.90 ± 0.37	0.47 ± 0.22	0.01•
Vitamin B12 (mg/day)	Before	2.2 ± 1.1	2.2 ± 1	0.13
	After 4 weeks	2.7 ± 1.5	1.9 ± 1.1	0.42
	End of Week 6	3.3 ± 2.6	1.9 ± 0.9	0.12
Folacin (mg/day)	Before	47 ± 19	75 ± 34	0.17
	After 4 weeks	54 ± 21	31 ± 13	0.01•
	End of Week 6	85 ± 78	23 ± 5	0.01•
Calcium (mg/day)	Before	441 ± 188	400 ± 198	0.55
	After 4 weeks	454 ± 243	340 ± 143	0.07
	End of Week 6	458 ± 250	316 ± 170	0.13
Phosphorous (mg/day)	Before	540 ± 170	496 ± 159	0.08
	After 4 weeks	543 ± 133	396 ± 176	0.02•
	End of Week 6	623 ± 195	373 ± 131	0.01•

or the associated tissue wasting, particularly that of the adipose mass [24]. Our findings demonstrated that omega-3 fatty acid supplementation can be quite effective in patients with gastric cancer. The intention-to-treat analysis of a recent prospective randomized trial in 200 patients with pancreatic cancer showed that intake of high-energy, high protein sip feeding (600 kcal/day, 32 g protein), irrespective of supplementation with omega-3-fatty acids and antioxidants resulted in stable body weights of the subjects [25]. Similar to previous studies we found that supplementation with omega-3 fatty acid significantly increased the body weight, energy, carbohydrate and protein intakes in gastric cancer patients [26,27]. Although Mario et al. observed no positive effects resulting from omega-3 fatty acids supplementation with regard to body weight and energy and dietary intakes in healthy subjects [28], most of the other studies have reported positive effects of this supplement [22,25]. An increase in body weight can be due to the fact that dietary supplementation of omega-3 fatty acids attenuates the adverse secondary effects to chemotherapy such as anorexia [29]. We

Table 3. Comparison of daily vitamin and mineral intakes between the placebo and supplement groups during the study (continued)

Magnesium (mg/day)	Before	82 ± 24	85 ± 34	0.38
	After 4 weeks	86 ± 26	72 ± 25	0.24
	End of Week 6	94 ± 20	50 ± 12	0.01●
Potassium (mg/day)	Before	1257 ± 362	1312 ± 407	0.52
	After 4 weeks	1361 ± 375	1290 ± 320	0.32
	End of Week 6	1408 ± 405	1014 ± 323	0.01●
Sodium (mg/day)	Before	210 ± 135	164 ± 117	0.08
	After 4 weeks	254 ± 115	125 ± 52	0.03●
	End of Week 6	274 ± 207	121 ± 39	0.01●
Copper (mg/day)	Before	210 ± 135	164 ± 117	0.08
	After 4 weeks	254 ± 115	125 ± 52	0.03●
	End of Week 6	274 ± 207	121 ± 39	0.01●
Iron (mg/day)	Before	210 ± 135	164 ± 117	0.08
	After 4 weeks	254 ± 115	125 ± 52	0.03●
	End of Week 6	274 ± 207	121 ± 39	0.01●
Selenium (µg/day)	Before	210 ± 135	164 ± 117	0.08
	After 4 weeks	254 ± 115	125 ± 52	0.03●
	End of Week 6	274 ± 207	121 ± 39	0.01●
Zinc (mg/day)	Before	210 ± 135	164 ± 117	0.08
	After 4 weeks	254 ± 115	125 ± 52	0.03●
	End of Week 6	274 ± 207	121 ± 39	0.01●

*Values are mean ±SD, *p<0.05 vs baseline, ** p<0.05 vs4 weeks in Repeated Measures ANOVA*
●p<0.05 in independent sample T-test between the two groups

observed that dietary supplementation with 3g of omega-3 fatty acids significantly increases the mean body weight, serum levels of albumin and transferrin, as well as intakes of energy and some macronutrients during chemotherapy. This finding confirms the positive effect of omega-3 fatty acids in improving the nutritional status of gastric cancer patients. Although the exact mechanism of omega-3 fatty acids in improving nutritional status and body weight of patients with gastric cancer is not known, it is suggested that omega-3 fatty acids can improve the nutritional status through influencing the nervous cell membrane, cytokine production and hypothalamic neurotransmitters [30]. Changes in the chemical composition of the cell membrane phospholipids may modify some properties of cell membranes such as secondary messages, neurotransmitters and transitional proteins and, thus, inhibit inflammatory cytokine production [28]. Since cytokines induce anorexia, body weight loss, wasting energy, loss of muscle protein and release of leptin, and damage the feeding centers in hypothalamus, their reduced production would improve the nutritional status of gastric cancer patients [31].

Conclusion

Our study demonstrated that the omega-3 fatty acids supplementation increases body weight and intakes of energy and some macronutrients in patients with gastric cancer and, thus, can be an excellent adjunct therapy for these patients during chemotherapy. Available evidence indicates that increased dietary intake of omega-3 fatty acids can lead to longer cancer survival by increasing energy and nutrient intakes and serum albumin level.

Acknowledgments

The authors gratefully acknowledge the Ardabil University of Medical Sciences (ArUMS) for their research funding and financial supports.

Conflict of interest

None of authors have conflict of interest.

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